LETTER TO THE EDITOR

Generalized erythema multiforme-like skin rash following the first dose of COVID-19 vaccine (Pfizer-BioNTech)

Dear Editor,

Since the outbreak of COVID-19 in December 2019, more than 4 million people have died worldwide. The global pandemic of COVID-19 has prompted each country to issue an emergency use authorization for COVID-19 vaccines. In South Korea, the Ministry of Food and Drug Safety authorized the administration of four vaccines: Pfizer-BioNTech (BNT162b2, New York, NY, USA), Moderna (mRNA-1273, Cambridge, MA, USA), Oxford–AstraZeneca (ChAdOx1, Cambridge, UK) and Johnson & Johnson's Janssen (JNJ-78436735, Beerse, Belgium). Although these vaccines were presumed to be safe, several nonspecific skin eruptions have been reported after the health system initiated public COVID-19 vaccination.[1] Here, we report a patient who developed *de novo* erythema multiforme (EM) following COVID-19 vaccination with BNT162b2.

A 78-year-old previously healthy woman presented to our clinic with a 2-day history of multiple targetoid erythematous plaques with severe itching over the entire body (Fig. 1). The patient received the first dose of COVID-19 vaccine (Pfizer-BioNTech) 12 days ago. Ten days after the vaccination, a skin rash appeared on the upper chest and spread rapidly to the remaining parts of the body, including oral mucosa, with bullous change and oozing. She also developed high fever and myalgia. She denied ever having herpes simplex virus (HSV) infection-related symptoms and did not take any new medication around the time of vaccination. She was hospitalized, and a 3-mm punch biopsy of the skin was performed. Pathologic examination revealed necrotic keratinocytes and subepidermal bullae with numerous lymphocytes infiltration in the dermoepidermal junction (Fig. 2). Clinically and histologically, the patient was diagnosed with EM. Systemic corticosteroid treatment with topical agents and oral antihistamine was started, and she was discharged after 1 week of treatment. During the subsequent 2-month treatment period, she experienced gradual resolution of the rash although post-inflammatory hyperpigmentation remained. She decided not to receive the second dose of COVID-19 vaccine because of concerns about the recurrence of severe skin rash.

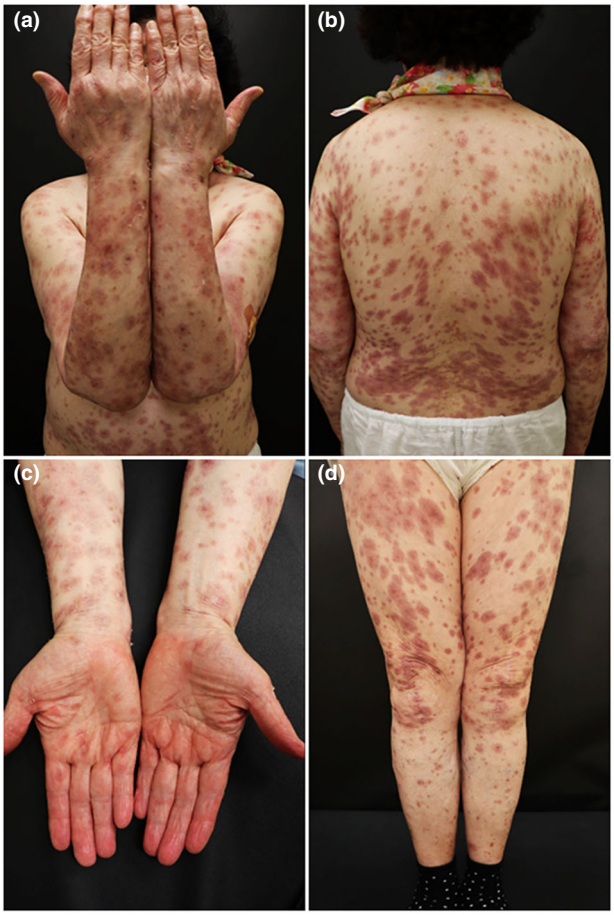

Figure 1 Multiple erythematous papules and concentric plaques on the (a) trunk and upper extremities, (b) back, (c) palms and (d) lower extremities.

Erythema multiforme is a skin disease triggered by infection or medication. In most cases, EM is associated with HSV infection; therefore, antiviral agents can be considered for treating recurrent cases.[2] Recently, Lavery *et al.*[3] reported a flare-up of pre-existing EM after COVID-19 vaccination with BNT162b2. Their patient had a history of recurrent herpes labialis treated with antiviral medication, and the lesions were limited to hands and feet. In contrast, our patient had no history of HSV infection and presented with a generalized EM eruption.

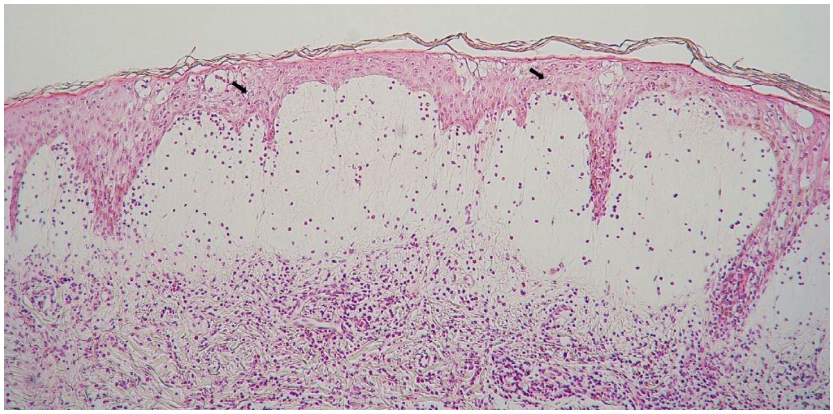

Figure 2 Haematoxylin and eosin (H&E, original magnification ×100) staining of a skin biopsy sample showing necrotic keratinocytes (black arrows), subepidermal bullae filled with lymphocytes and eosinophils, and dermal infiltration of numerous lymphocytes attacking the interface.

Some cases of EM have been reported after other vaccinations, including diphtheria/pertussis/tetanus, human papillomavirus and measles–mumps–rubella.[4–6] Su *et al.*[7] analysed post-vaccination surveillance data, collected from 1999 to 2017, for EM, Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Of 466 027 cases, EM accounted for 0.2%. The median time from vaccination to the onset of EM was 6 days. Most adverse events occurred within 14 days of vaccination. Therefore, the temporal association between the COVID-19 vaccine and EM in our case cannot be excluded.

It is unclear how vaccines trigger EM/SJS/TEN. Vaccine antigens are thought to induce cell-mediated inflammation and stimulate immune reactions. The activation of T helper type 1 cells leads to cytokine secretion, which is responsible for keratinocyte necrosis, subsequent epidermal antigen exposure and T-cell recruitment.[8] The same cascade is involved in the pathophysiology of EM/SJS/TEN, although the specific causative antigen or predisposing factor in affected patients is still unknown. Although these diseases may be life-threatening, considering the number of vaccinated people, the incidence is rare. There is evidence suggesting that the second dose of vaccine may cause the same adverse events, although they are mild in most cases.[1,9] Therefore, it cannot be the reason for prohibiting or discouraging vaccinations, and surveillance of skin adverse events should be continued.

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The patient in this manuscript has given written informed consent to publication of her case details.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Data availability statement

Data openly available in a public repository that issues datasets with DOIs.

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